UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
10/620,725			

EXAMINER
KISHORE

ART UNIT	PAPER NUMBER
1615	

DATE MAILED:

INTERVIEW SUMMARY

All participants (applicant, applicant's representative, PTO personnel):

(1) G.S. KISHORE (3) _____

(2) KATE MURASHIGE (4) _____

Date of Interview 11-9-05

Type: ☐ Telephonic ☐ Televideo Conference ☒ Personal (copy is given to ☐ applicant ☒ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No If yes, brief description: _____

Agreement ☐ was reached. ☒ was not reached.

Claim(s) discussed: Proposed claims

Identification of prior art discussed: Prior art on record.

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: The attorney indicated that the claims (Proposed) have been amended to indicate that the drug is in the lipid/surfactant layer & not in the interior of the nanoparticle and therefore, overcome the inherency. The examiner will consider this argument.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary. A FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has are ready been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

Examiner Note: You must sign this form unless it is an attachment to another form.

G S Kishore

Gollamudi S. Kishore, PhD
Primary Examiner
Group 1600

FORM PTOL-413 (REV. 2-98)

Manual of Patent Examining Procedure, Section 713.04 Substance of Interview must Be Made of Record

Except as otherwise provided, a complete written statement as to the substance of any face-to-face or telephone interview with regard to an application must be made of record in the application, whether or not an agreement with the examiner was reached at the interview.

§1.133 Interviews

* * * * *

(b) In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111 and 1.135. (35 U.S.C. 132)

§ 1.2. Business to be transacted in writing. All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete a two-sheet carbon interleaf Interview Summary Form for each interview held after January 1, 1978 where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks in neat handwritten form using a ball point pen. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, pointing out typographical errors or unreadable script in Office actions or the like, or resulting in an examiner's amendment that fully sets forth the agreement are excluded from the interview recordation procedures below.

The Interview Summary Form shall be given an appropriate paper number, placed in the right hand portion of the file, and listed on the "Contents" list on the file wrapper. In a personal interview, the duplicate copy of the Form is removed and given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephonic interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication.

The Form provides for recordation of the following information:

- Application Number of the application
- Name of applicant
- Name of examiner
- Date of Interview
- Type of Interview (personal or telephonic)
- Name of participant(s)) (applicant, attorney or agent, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the claims discussed
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). (Agreements as to allowability are tentative and do not restrict further action by the examiner to the contrary.)
- The signature of the examiner who conducted the interview
- Names of other Patent and Trademark Office personnel present.

The Form also contains a statement reminding the applicant of his responsibility to record the substance of the interview.

It is desireable that the examiner orally remind the applicant of his obligation to record the substance of the interview in each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form or in an attachment to the Form, the examiner should check a box at the bottom of the Form informing the applicant that he need not supplement the Form by submitting a separate record of the substance of the interview.

It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview:

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner. The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he feels were or might be persuasive to the examiner,
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete or accurate, the examiner will give the applicant one month from the date of the notifying letter to complete the reply and thereby avoid abandonment of the application (37 CFR 1.135(c)).

Examiner to Check for Accuracy

Applicant's summary of what took place at the interview should be carefully checked to determine the accuracy of any argument or statement attributed to the examiner during the interview. If there is an inaccuracy and it bears directly on the question of patentability, it should be pointed out in the next Office letter. If the claims are allowable for other reasons of record, the examiner should send a letter setting forth his or her version of the statement attributed to him. If the record is complete and accurate, the examiner should place the indication "Interview record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

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To: **Examiner Gollamudi S. Kishore, Ph.D.**
U.S. Patent and Trademark Office
Art Unit 1615

Facsimile: **571-273-0598**
Telephone: 571-272-0598

From: Kate H. Murashige

Date: November 4, 2005

We are transmitting a total of **33** pages (including this page).
Original or hard copy to follow if this box is checked ☐.

Preparer of this slip has confirmed that facsimile number given is correct: 9184/MLC3

Comments: Serial No: 10/620,725
Our reference: 53251-20004.01
and
Serial No. 10/264,538
Our reference: 53255-20001.00

Thank you for agreeing to an interview these cases on **Wednesday, November 9** at **1:30 p.m.**

Here are some draft responses that could be discussed.

I look forward to seeing you.

Kate H. Murashige

IN THE EVENT YOU DO NOT RECEIVE ALL THE PAGES, PLEASE CALL MARIAN CHRISTOPHER AT (858) 720-7970, AS SOON AS POSSIBLE

sd-287389

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: November ___, 2005 Signature: _____
(Marian L. Christopher)

Docket No.: 532512000401
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Gregory M. LANZA et al.

Application No.: 10/620,725

Filed: July 15, 2003

For: LIGAND-TARGETED EMULSIONS CARRYING BIOACTIVE AGENTS

Confirmation No.: 1157

Art Unit: 1615

Examiner: Gollamudi S. Kishore, Ph.D.

analogy w. liposomes
Review Chaxo -
+ no reason
to enhance
in lungs

AMENDMENT UNDER 37 C.F.R. § 1.116

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DRAFT

Fig 3 is
pretty
impressive

Dear Sir:

This is in response to an Office Action herein, mailed 1 August 2005, time for response to which was set to expire 1 November 2005. A petition for an extension of time of one (1) month until 1 December 2005 is attached hereto, along with the required fee. The pending claims were rejected and the rejection was made final. Careful consideration has been given to the grounds for rejection, and the following amendment and discussion are offered in response. Reconsideration and entry of the amendment are respectfully requested.

SPECIFICATION AMENDMENTS

Please amend the first paragraph of the application, under Cross-Reference to Related Application, to read

This application is a continuation of U.S. Utility Application Serial No. 09/697,796 filed 27 October 2000 and now U.S. patent 6,673,963. The contents of this application [[~~is~~]] are incorporated herein by reference.

CLAIM AMENDMENTS

1-70. (canceled)

71. (currently amended): A method to deliver a drug to a target tissue or organ, which method comprises

administering to a subject containing said tissue or organ a composition of nanoparticles,

said nanoparticles comprising a fluorocarbon core coated with a lipid/surfactant layer,

wherein said drug is contained in said layer and not carried or deposited in the interior of said nanoparticle; and

wherein said coated particles are coupled to a targeting ligand that binds to a moiety on or in said tissue or organ; and

wherein said targeting ligand effects prolonged contact between the lipid bilayer of cells of said tissue or organ with the lipid/surfactant layer of said coated particles such that delivery of the drug to the tissue or organ is facilitated.

72. (previously presented): The method of claim 71, wherein said drug is a nucleic acid and said surfactant/lipid monolayer comprises at least one cationic lipid.

73. (previously presented): The method of claim 72, wherein said nanoparticles further comprise at least one anionic lipid.

74. (previously presented): The method of claim 71, wherein said prolonged contact is localized to the surface of cells contained in said tissue or organ.

75. (previously presented): The method of claim 71, wherein said targeting ligand is selected from the group consisting of antibodies, antibody fragments, peptides, asialoglycoproteins, polysaccharides, aptamers, nucleic acids, peptidomimetics, and drugs.

76. (previously presented): The method of claim 75, wherein said targeting ligand is an antibody.

77. (previously presented): The method of claim 71, wherein said fluorocarbon is perfluorooctylbromide.

78. (previously presented): The method of claim 71, wherein said fluorocarbon is a liquid with a boiling point above 30°C.

79. (previously presented): The method of claim 78, wherein said fluorocarbon liquid has a boiling point above 90°C.

80-81 (canceled)

82. (previously presented): The method of claim 71, wherein said lipid/surfactant layer is composed of a material selected from the group consisting of a natural or synthetic phospholipid, a fatty acid, cholesterol, lysolipid, sphingomyelin, tocopherol, glucolipid, stearylamine, cardiolipin, a lipid with ether or ester linked fatty acids and a polymerized lipid.

83. (previously presented): The method of claim 71, wherein said surfactant is at least one nonionic and/or amphoteric surfactant.

84. (previously presented): The method of claim 71, wherein said composition contains an emulsifying and/or solubilizing agent.

85. (previously presented): The method of claim 71, wherein said coated nanoparticles have a diameter in the range of 0.01 to 10 microns.

86. (previously presented): The method of claim 85, wherein said coated nanoparticles have a diameter in the range of approximately 0.1 to 0.5 microns.

87. (currently amended): The method of claim 71 wherein the drug is ~~an antineoplastic,~~ an anti-inflammatory, an antirheumatic, a neuromuscular blocker, a sedative, ~~an anticoagulant,~~ an antiallergic drug, ~~an antianginal,~~ a hormone, an anti-helmintic, an antimalarial, an antituberculosis

drug, an immune serum, an antitoxin, an antivenom, a rabies prophylaxis product, a bacterial vaccine, or a viral vaccine.

88. (previously presented): The method of claim 71 wherein the drug is an androgen, a progestin, an estrogen, or an antiestrogen.

89. (currently amended): The method of claim 71 wherein the drug is spiroplatin, carboplatin, mitomycin, ansamitocin, bleomycin, cytosine arabinoside, arabinosyl adenine, mercaptopolylysine, busulfan, chlorambucil, melphalan, mercaptopurine, mitotane, procarbazine hydrochloride dactinomycin (actinomycin D), rapamycin, manumycin A, TNP-470, plicamycin (mithramycin), aminoglutethimide, estramustine phosphate sodium, flutamide, leuprolide acetate, megestrol acetate, tamoxifen citrate, testolactone, trilostane, amsacrine (m-AMSA), interferon α-2a, interferon α-2b, teniposide (VM-26), vinblastine sulfate (VLB), bleomycin sulfate, hydroxyurea, procarbazine, dacarbazine, colchicine, or paclitaxel or other taxane ~~or doxorubicin~~.

90. (previously presented): The method of claim 71 wherein the drug is an aminoglycoside, a xanthine derivative, theophylline, aminophylline, a chelating agent, a mercurial diuretic, a cardiac glycoside, glucagon, parenteral iron, hemin, a hematoporphyrin, muramyldipeptide, muramyltripeptide, a microbial cell wall component, a lymphokine, a synthetic dipeptide N-acetyl-muramyl-L-alanyl-D-isoglutamine, ketoconazole, nystatin, griseofulvin, flucytosine (5-fc), miconazole, amphotericin B, ricin, a cyclosporin, a β-lactam antibiotic, a growth hormone, a melanocyte stimulating hormone, estradiol, beclomethasone dipropionate, betamethasone, betamethasone acetate, or betamethasone sodium phosphate.

91. (currently amended): The method of claim 71 wherein the drug is betamethasone disodium phosphate, betamethasone sodium phosphate, cortisone acetate, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, flunisolide, hydrocortisone, hydrocortisone acetate, hydrocortisone cypionate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, paramethasone acetate, prednisolone, prednisolone acetate, prednisolone sodium

phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, triamcinolone hexacetonide, fludrocortisone acetate, oxytocin, vasopressin, vitamins, retinoids, manganese super oxide dismutase, alkaline phosphatase, ~~anti-allergic agents,~~ phenprocoumon, heparin, propranolol, or glutathione.

92. (previously presented): The method of claim 71 wherein the drug is isoniazid, capreomycin sulfate cycloserine, ethambutol hydrochloride ethionamide, pyrazinamide, rifampin, streptomycin sulfate, acyclovir, amantadine azidothymidine, ribavirin, vidarabine monohydrate, diltiazem, nifedipine, verapamil, erythritol tetranitrate, isosorbide dinitrate, nitroglycerin (glyceryl trinitrate), pentaerythritol tetranitrate, dapsone, chloramphenicol, neomycin, cefaclor, cefadroxil, cephalexin, cephradine erythromycin, clindamycin, lincomycin, amoxicillin, ampicillin, bacampicillin, carbenicillin, dicloxacillin, cyclacillin, picloxacillin, hetacillin, methicillin, nafcillin, oxacillin, penicillin including penicillin G and penicillin V, ticarcillin rifampin and tetracycline, diflunisal, ibuprofen, indomethacin, meclofenamate, mefenamic acid, naproxen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, tolmetin, aspirin, chloroquine, hydroxychloroquine, metronidazole, quinine, meglumine antimonite, penicillamine, paregoric, codeine, heroin, methadone, morphine and opium, deslanoside, digitoxin, digoxin, digitalin and digitalis, atracurium mesylate, gallamine triethiodide, hexafluorenium bromide, or metocurine iodide.

93. (previously presented): The method of claim 71 wherein the drug is pancuronium bromide, succinylcholine chloride (suxamethonium chloride), tubocurarine chloride and vecuronium bromide, amobarbital, amobarbital sodium, aprobarbital, butabarbital sodium, chloral hydrate, ethchlorvynol, ethinamate, flurazepam hydrochloride, glutethimide, methotrimeprazine hydrochloride, methyprylon, midazolam hydrochloride, paraldehyde, pentobarbital, pentobarbital sodium, phenobarbital sodium, secobarbital sodium, talbutal, temazepam and triazolam, bupivacaine hydrochloride, chloroprocaine hydrochloride, etidocaine hydrochloride, lidocaine hydrochloride, mepivacaine hydrochloride, procaine hydrochloride and tetracaine hydrochloride, droperidol, etomidate, fentanyl citrate with droperidol, ketamine hydrochloride, methohexital sodium, or thiopental sodium.

REMARKS

First, applicants wish to express their appreciation for the apparent withdrawal of finality of the previous Office action. Applicants understand that this is because certain claims, claims 87-93 were not considered in that action; the present action takes account of them.

The claims have been amended for clarity only. The Examiner has pointed out, on page 4 of the Official action, that the claims "do not exclude the presence of the active agent in the interior." Applicants have based their arguments on the concept that this is the intent of the claims, and this has now been made explicit. Because this has been the basis for applicants' arguments, it is believed no new issues are raised, and that entry of the amendment, though made after final, is proper. Substantially *in haec verba* support for this amendment is found on page 7 of the specification at lines 16-18. The remaining amendment to claim 71 coordinates the effect of the method with the preamble and does not add new matter. Substantially *in haec verba* support for this amendment, also, is found on page 6, lines 12-15.

The proposed amendment to claim 87 is intended to place this claim in better position for allowance or appeal. Classes of drugs on the list set forth in claim 87 have simply been deleted, and nothing has been added. Similarly, doxorubicin has been deleted from the list of drugs in claim 89 and antiallergic agents has been deleted from the list of drugs in claim 91 as inconsistent in scope with individual drugs listed previously in that claim.

Clearly no new matter has been added and entry of the amendment is respectfully requested, applicants sincerely believe that the amendments place the claims in a position for allowance and request that the Examiner exercise his discretion to enter them.

There are two outstanding grounds for rejection: claims 71-79 and 82-86 are rejected as assertedly anticipated by any one of three substantially equivalent Lanza patents; all claims (claims 71-79 and 82-93) were rejected as assertedly obvious over any of the Lanza patents alone or in combination with Adler-Moore (U.S. 5,656,287).

Before addressing these rejections directly, applicants point out that the present invention resides in the discovery, clearly not appreciated or described by the disclosure in the primary documents, that having the biologically active agent or drug reside in the surfactant/lipid layer of the nanoparticles and targeting the nanoparticles to the desired tissue or organ permits prolonged contact between the lipid/surfactant layer and the lipid bilayer of the cells contained in the tissue or organ such that their intermingling permits and facilitates delivery of the drug. Nothing of this effect is noted in any of the Lanza patents. Nothing is said in any of the Lanza patents with respect to the location of the drug in the lipid/surfactant layer. Thus, the only manner in which Lanza can anticipate the present invention is under the circumstance that this would be inherent.

The Office has asserted that inherency exists, because in the case of liposomes which have lipid bilayers surrounding an aqueous interior, hydrophobic drugs would find themselves in the lipid bilayers. Therefore, the Office concludes that the description of Lanza inherently requires the presence of hydrophobic drugs, at least, in the lipid/surfactant layer as required by the claims. Applicants have pointed out that the analogy does not hold because the nanoparticles are hydrophobic throughout. For this reason, the inherency asserted by the Office is not supported by the rationale provided.

The proposed amendment to the claims clarifies that the drug is contained in the lipid/surfactant layer "and not carried or deposited in the interior of said nanoparticles." This is completely supported by the specification as set forth above.

Turning, now, to the rejections as they are presented, claims 71-79 and 82-86 were rejected as assertedly anticipated by three Lanza patents, all members of the same family, that are of record. The Office points out that similar compositions to those contained in the claims were used and that the disclosure in each case indicates that the compositions may contain biologically active agents, naming certain specific drugs. The Office states that "it is known in the art that lipophilic agents get incorporated in the lipid bilayer of the liposomes and the hydrophilic agents in the interior." The Office acknowledges the argument in the previous response that the present compositions are not liposomes so that there is no aqueous interior or bilayer; rather both the interior of the particles and the lipid/surfactant outer layer are hydrophobic, but maintains the rejection based on this analogy. It is not clear how this is reasonable, since there is an admission of record that the analogy is flawed.

Applicants do not understand at least part of the reason given for finding their arguments not persuasive – "since whether the lipid layer is a bilayer or single layer, the property of the lipophilic compounds is to sequester into the lipid." Applicants did not argue any significance to the lipid layer being a single layer as opposed to a bilayer. The Office asserts that the presence of the lipophilic agent in both the hydrophobic interior and the lipid layer is implicit in Lanza and that the instant claims do not exclude the presence of the active agent in the interior. Applicants do understand this aspect of the Office's position, and the claims have been proposed to be amended to obviate this basis for rejection by simply clarifying claim 71. Again, respectfully, applicants have maintained this is the meaning of the claim all along, so no new issue is now raised.

Since it is a requirement of the claims that the drug reside in the lipid/surfactant layer, and not in the interior of the particle or anywhere else associated with the particle, the finding of inherent anticipation should be reviewed in light of the case precedent for elements required to find inherency. The standard is quite high, as applicants are certain the Office is aware. Over and over, the Federal Circuit has cited the principle set forth in *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F2d 1264, 20 USPQ2d 1746 (Fed. Cir. 1991) which was actually quoted from two earlier CCPA cases – *In re Oelrich*, 666 F2d 578, 212 USPQ 323, (CCPA 1981) which in turn quoted *Hansgirg v. Kemmer,* 40 USPQ 665 (CCPA 1939).

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.

It must be evident that this standard is one that has been followed by the Appeals Court in patent cases for more than half a century. How, then, is this standard to be interpreted in light of facts in individual cases? Perhaps closest in fact pattern to the present case is the holding in *Glaxo, Inc. v. Novopharm, Ltd.*, 52 F3d 1043, 34 USPQ2d 1565 (Fed. Cir. 1995). This case concerned Zantac®. An initial patent on this molecule described the preparation of what came to be known as Form 1. Glaxo later found that a different polymorphic form, designated Form 2, had superior properties. A later patent was filed and issued on Form 2. In an infringement suit against Novopharm, triggered by Novopharm's Abbreviated New Drug Application (ANDA), paragraph 4 certification, Novopharm asserted that one of the examples in Glaxo's earlier patent resulted in Form 2, and although this was not recognized, there was inherent anticipation. In evaluating the

proceedings below, the Federal Circuit noted that Novopharm's expert "performed the process disclosed in Example 32 of the '658 (first) patent thirteen times and each time they made Form 2 crystals, not Form 1 as Glaxo claims."

This, however, was *not* good enough to justify a holding of inherent anticipation:

> But the District Court found that the practice of Example 32 could yield crystals of *either* polymorph. It specifically found that Glaxo's David Cullen originally made Form 1 by practicing Example 32 and that Glaxo's expert, Nicholas Crouch, did so as well.

Based on this evidence, the District Court held that anticipation did not exist, and the Federal Circuit affirmed. Thus, the finding of lack of inherency was justified even if there was evidence that sometimes (but not always) Form 2 was obtained by following the directions in the earlier patent. The legal principle behind this affirmation was explicitly stated to be that quoted above from *Continental Can.*

Comparing *Glaxo* to the situation here, it appears that the possibilities are even more open. There are no directions in Lanza for preparing the emulsions of coated perfluorocarbon nanoparticles so as to include a therapeutic agent. The single paragraph that describes this simply says, "[t]he ligand-based binding systems of the invention may also be applied to provide a chemotherapeutic agent or gene therapy system combined with ultrasonic imaging." No other instructions as to how the therapeutic agent or gene therapy delivery system is to be included are found. It would clearly not be suggested to the ordinary practitioner to include the drug in the lipid/surfactant layer as directed in the present application and as illustrated by the examples therein.

The practitioner, lacking the guidance of the present invention and therefore not understanding that residence in the lipid layer and prolonged contact with the lipid cellular membrane would enhance drug delivery, would have no incentive to use the particular method

taught in the present application to include the drug in the emulsion. Many other methods are available. For example, the most straightforward way to include a hydrophilic drug would be to attach it to a lipid anchor that would reside in the lipid/surfactant layer, and permit the drug to reside in the aqueous medium outside the particle. This would not result in the drug being included in the lipid layer as required by the claims – indeed, a spacer might very well be included to distance the drug even farther from the outer surface of the layer. Second, the drug could be suspended in the perfluorocarbon core, including crystalline forms of the drug that could be intimately mixed therewith prior to the preparation of the nanoparticles. This would result in the majority of the drug being included in the core rather than in the lipid layer. Again, unless the practitioner were aware of the present invention, there would be no incentive to ensure that it was included in the outer layer. Still another approach that would occur to the practitioner is to attach a drug using the same biotin/avidin linking system described in Lanza. Thus, the drug might be coupled to avidin and secured to the particles through biotin-related components of the layer. Again, the drug would not reside in the lipid layer, but in the medium outside of it.

Further, there are no limitations in Lanza on any linker that couples the targeting ligand to the particles. Indeed, a biotin/avidin/biotin bridge as described in Lanza would distance the particles sufficiently from the targeted tissue so that the lipid/surfactant layer would fail to contact the cellular membrane.

Thus, depending on how a practitioner actually constructed the emulsions to include the therapeutic agent (and indeed, the targeting ligand), the therapeutic agent might or might not reside in the lipid/surfactant layer. Since no instructions are provided in Lanza, any method of construction, including those set forth above which clearly do not have the required result, can be

used. Thus, the disclosure of Lanza falls far short of the standard enunciated in *Continental Can* and applied in an entirely analogous way in *Glaxo*.

For these reasons, it is believed that the invention as now proposed to be claimed in claims 71-79 and 82-86 is not anticipated.

All claims of the application were rejected as assertedly obvious over any of the Lanza patents either alone or in combination with Adler-Moore.

Adler-Moore concerns liposomes, which are not the subject of the present invention. The process of preparation of liposomes may be similar to that in the present application, but it is not similar enough – the resultant composition is entirely different, as the present application concerns nanoparticles with hydrophobic cores and Adler-Moore concerns liposomes. The method of Lanza does not, as asserted by the Office, involve addition of an aqueous medium to the lipid mixture except in the presence of the perfluorooctylbromide which effects coating of the perfluorooctylbromide with the lipid/surfactant and formation of an emulsion. No liposomes are formed, as applicants are certain the Office would acknowledge. Thus, Adler-Moore appears completely irrelevant.

As to obviousness with regard to the Lanza documents alone, there has been no showing that Lanza suggests delivering drugs by encapsulating them in the outer layer of hydrophobic nanoparticles which are targeted to desired tissues or organs as required by the claims. There is no suggestion in Lanza that targeting hydrophobic particles which contain drugs substantially exclusively in the lipid/surfactant coating and permitting prolonged contact with the bilayers in the cells at the surface of the target tissues or organs would be an effective method to facilitate drug

delivery. Thus, if inherent anticipation cannot be shown, none of the Lanza documents defeats patentability of the present claims. The present basis for rejection does not encompass anticipation.

As noted above, applicants believe that the Office has failed to show that any claim is inherently anticipated by any Lanza document. However, there are clearly some claims that cannot possibly be considered inherently anticipated. These include claims 87-93; indeed, the Office has never asserted that these claims are anticipated.

Thus, claims 87-93 are clearly free of the cited art, regardless of the fate of claims 71-79 and 82-86 with respect to the rejection for anticipation.

Conclusion

Claim 71 has been proposed to be amended to clarify that the drug to be delivered resides in the lipid/surfactant layer and not in the interior of the nanoparticles. This limitation is completely supported by the specification as noted. The residence of the drug in the lipid/surfactant layer, and the prolonged contact required and achieved by targeting the particles to the desired tissue or organ results in facilitating drug delivery. None of this is suggested by any of the documents cited by the Office. The proposed amendment to claim 71 clearly distinguishes all claims from Lanza. Applicants have set forth the relevant case law for inherent anticipation and demonstrated that Lanza does not teach a method to construct the particles which would inevitably result in a drug residing in the lipid/surfactant layer, as would be required for inherent anticipation of the invention as claimed. There is no assertion that claims 87-93 are anticipated by Lanza and so clearly these claims are free of the art, regardless of what the view of the Office might be regarding claims 71-79 and 82-86. Therefore, applicants believe all claims are in a position for allowance and respectfully request that claims 71-79 and 82-93 be passed to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 532512000401.

Respectfully submitted,

Dated: November ___, 2005 By: _____

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